

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/22	A1	(11) International Publication Number: WO 99/29305 (43) International Publication Date: 17 June 1999 (17.06.99)
(21) International Application Number: PCT/US98/25630 (22) International Filing Date: 3 December 1998 (03.12.98) (30) Priority Data: 08/985,986 5 December 1997 (05.12.97) US (71) Applicant: DURAMED PHARMACEUTICALS, INC. [US/US]; 5040 Duramed Drive, Cincinnati, OH 45213 (US). (72) Inventors: ZHANG, Guohua; 1 Doric Avenue, Parsippany, NJ 07054 (US). PINNAMARAJU, Prasad; 243 Horizon Drive, Edison, NJ 08817 (US). ALI, Muhammad; 236 Michelle Circle, Edison, NJ 08820 (US). (74) Agents: MARSH, James, H., Jr. et al.; Shook, Hardy & Bacon L.L.P., One Kansas City Place, 1200 Main Street, Kansas City, MO 64105-2118 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: SUSTAINED RELEASE FORMULATION CONTAINING THREE DIFFERENT TYPES OF POLYMERS AND TABLET FORMED THEREFROM		
(57) Abstract <p>Depot drug formulations include the pharmaceutical itself and a three component release rate controlling matrix composition. The three components of the matrix composition are (1) a pH dependent gelling polymer such as an alginate component; (2) an enteric polymer component, such as Eudragit® L or S; and (3) a pH independent gelling polymer, such as hydroxy propyl methyl cellulose or polyethylene oxide. The drug release rate can be adjusted by changing the amount of one or more of these components of the composition.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

**SUSTAINED RELEASE FORMULATION CONTAINING
THREE DIFFERENT TYPES OF POLYMERS
AND TABLET FORMED THEREFROM**

Cross Reference to Related Application

5 This application is a continuation-in-part of prior copending application serial no. 08/395,565, filed March 1, 1995, the entirety of the disclosure of which is hereby specifically incorporated herein by reference.

Field of The Invention

10 The present invention is directed to formulations for preparing sustained release drug forms useful for releasing pharmaceuticals at controlled rates, generally in the stomachs and/or gastrointestinal tracts of hosts. In particular the invention relates to an improved depot drug form useful in connection with preparing sustained release tablets.

Background of the Invention

15 A zero order release profile for a drug from its controlled release dosage form sometimes is desirable in clinical use. The technology used to formulate zero order release dosage forms is well documented. The entrapment of a drug in a matrix is a common approach to formulate sustained release tablets with a zero order release profile.

20 It has been reported that depot drug formulations for controlled release of pharmaceutical drugs may be prepared using alginates alone (see U.S. patent no. 5,132,295), using combinations of alginates and polyacrylates (see U.S. patent no. 5,230,901) and using combinations of alginates and a pH independent hydrocarbon gelling agent, such as, for example, hydroxypropylmethyl cellulose (see U.S. patent no. 4,792,452). It is also known that the use of alginates alone for this purpose often presents difficulties in tableting, film coating and storage.

25 Adding polyacrylates to the alginate formulation overcomes these difficulties to some extent; however, tablets formed using alginates and polyacrylates often have a pH dependent dissolution profile. In a low pH environment, alginates and polyacrylates do not swell and/or dissolve properly. This leads to drug release by a diffusion mechanism through non-viscous capillaries resulting in a different dissolution rate than in a high pH
30 environment. On the other hand, in a high pH environment, alginates swell and become soluble while polyacrylates may or may not do the same. This leads to drug release both by erosion and diffusion at a rate which is different than the low pH release rate.

- 2 -

In formulations which include an alginate and a pH independent gelling polymer such as, for example, hydroxypropylmethyl cellulose, such polymers hydrate at low pH levels to create a viscous gel layer for drug release. At high pH levels, however, tablets become smaller and smaller during drug release due to polymer erosion, and this leads to a reduction in surface area which may affect dissolution rate.

Summary of the Invention

A novelty of the present invention is the provision of a sustained release formulation which reduces, and perhaps eliminates these problems completely. In particular the invention provides a controlled release drug formulation which includes 1) a pH dependent gelling polymer such as, for example, an alginate material, a carboxyvinyl polymer or a sodium salt of carboxymethyl cellulose, 2) an enteric polymer, such as, for example, a cellulose acetate phthalate, a cellulose phthalate hydroxy propyl methyl ether, a polyvinyl acetate phthalate, a hydroxy propyl methyl cellulose acetate succinate, a cellulose acetate trimellitate, a shellac or a polyacrylate material such as Eudragit® L or Eudragit® S, and 3) a pH independent gelling polymer, such as, for example, a hydroxy propyl methyl cellulose, a hydroxy propyl ethyl cellulose, a hydroxy propyl cellulose, a hydroxy ethyl cellulose, a methyl cellulose, a xantham gum or a polyethylene oxide. Such a combination of ingredients facilitates manufacturing procedures and improves drug dissolution profile.

In the formulation in accordance with the present invention, the pH dependent gelling polymer provides excellent binding and controlled release characteristics thereby facilitating the manufacturing processes. During dissolution, the pH independent gelling polymer hydrates to form a gel layer to control drug release at low pH levels. At high pH levels, the enteric polymer increases erosion rate so as to maintain a constant dissolution rate regardless of tablet size. So reduction in tablet size does not reduce release rate. Thus, the formulations of the present invention provide improved drug release profiles compared with the prior art formulations described above.

Detailed Description of the Preferred Embodiments

The present invention provides sustained release tablets formulated with a mixture of a pharmaceutical composition, a pH dependent gelling polymer, an enteric polymer and a pH independent gelling polymer from which the pharmaceutical composition may

be released at a controlled rate. In a particularly preferred form of the invention, the formulation may be used to provide a depot drug form for controlled release of a verapamil containing pharmaceutical composition. However, the formulation is also useful in connection with a variety of other pharmaceutical or active compositions, including water soluble compositions, water sparingly soluble compositions and water insoluble compositions, and therefore the invention should not be considered as being limited by the exact composition and/or nature of the pharmaceutical or other active composition which is released under controlled conditions therefrom.

In a preferred form, the formulation of the invention may contain 1) a pH dependent gelling polymer such as an alginate component in the form of a water soluble salt of an alginic acid having a viscosity within the range of from about 60 to about 10,000 centipoises, and preferably from about 100 to about 6,000 centipoises, in a 2% by weight water solution at 25° C, as measured by a Brookfield LV viscometer; 2) an enteric polymer composition component, such as a cellulose derivative or a methacrylic acid copolymer (preferably Eudragit® L/S); and 3) a pH independent gelling polymer component, such as a cellulose derivative or polyethylene oxide, having a viscosity within the range of from about 10 to about 100,000 centipoises, and preferably from about 50 to about 15,000 centipoises in a 2% by weight water solution at 20° C.

The active drug content in the overall tablet formulation may preferably range from about 0.5% to about 70% by weight. The total amount of the gelling and enteric polymers in the overall tablet formulation may preferably range from about 8% to about 65% by weight. The total amount of the pH dependent gelling polymer in the overall tablet formulation may preferably range from about 2% to about 60% by weight. The total amount of the pH independent polymer in the overall tablet formulation may preferably range from about 2% to about 55% by weight. The total amount of the enteric polymer in the overall tablet formulation may preferably range from about 1% to about 55% by weight.

Suitable enteric polyacrylate materials are described, for example, in U.S. letters patent no. 5,230,901, the entirety of the disclosure of which is incorporated herein by reference. In this regard, the term polyacrylate is used herein to encompass the polyacrylates, the polymethacrylates and the copolymers of acrylic and methacrylic acid disclosed in the '901 patent. These materials are also described in, for example, Houben-Weyl, Methoden der organischen Chemie, Thieme-Verlag, Stutt, 1961. Products which

are commercially available under the name Eudragit®, for example Eudragit® L and Eudragit® S, are particularly suitable. Other suitable enteric polymers include, for example, cellulose derivatives such as cellulose acetate phthalate, cellulose phthalate hydroxy propyl methyl ether, hydroxy propyl methyl cellulose acetate succinate, 5 cellulose acetate trimellitate, and substances such as polyvinyl acetate phthalate, shellac and polymethacrylates, etc.

Other ingredients which may be optionally included in the formulation of the invention include 1) one or more binders such as, for example, povidone (polyvinylpyrrolidone), modified starch, low viscosity hydroxypropylmethyl cellulose, 10 etc.; 2) one or more fillers such as, for example, microcrystalline cellulose, lactose, starch, calcium sulfate, etc.; 3) one or more lubricants such as, for example, magnesium stearate, stearic acid, etc.; 4) one or more coating film formers such as, for example, Opadry (a hydroxypropylmethyl cellulose based coating system); and 5) one or more colorants such as, for example, FD&C green dye. The binder materials may be present 15 in an amount up to about 10% by weight of the entire formulation and the lubricant materials may be present in an amount within the range of from about 0.1% to about 5.0% by weight of the entire formulation.

In the specific examples set forth below, three specific embodiments of the invention for releasing verapamil HCl are exemplified. These embodiments have been 20 designated A, B and C.

SPECIFIC EXAMPLES OF PREFERRED EMBODIMENTS

<u>COMPONENT</u>		<u>AMOUNT OF COMPONENT IN EACH EMBODIMENT</u>		
		<u>A</u>	<u>B</u>	<u>C</u>
	1. VERAPAMIL HCL	240 MG	120 MG	240 MG
25	2. SODIUM ALGINATE	250 MG	80 MG	200 MG
	3. HYDROXYPROPYLMETHYL CELLULOSE	50 MG	15 MG	—
	4. POLYETHYLENE OXIDE	—	—	60 MG
30	5. METHACRYLIC ACID COPOLYMER (®Eudragit L/S)	120 MG	30 MG	100 MG
	6. POVIDONE	50 MG	25 MG	40 MG

- 5 -

7. MICROCRYSTALLINE CELLULOSE	60 MG	80 MG	80 MG
8. MAGNESIUM STEARATE	5 MG	2 MG	5 MG

Items 1 through 7 listed above are mixed in a mixer such as a high shear mixer granulator or planetary mixer to obtain homogeneity. The mix is then granulated in water or other suitable granulation fluids and dried in a dryer. The dried granular mass is then milled and then item 8 (a lubricant) is added during milling. The lubricated granular mass is then compressed into tablets using a tablet press. The foregoing steps are conventional steps used in the tablet forming industry.

In the preferred embodiments set forth above, the formulations of the invention have particular utility in the preparation of sustained release tablets of verapamil. However, the invention is not limited to use in connection with this drug only. Tablets containing other drugs requiring sustained release are as well within the intended scope of the invention. It is contemplated that the sustained release formulations of the invention have utility in connection with drugs which are water soluble, water sparingly soluble or water insoluble. For example, suitable pharmaceutical drugs which may require sustained release and which therefore are within the scope of the present invention are listed in U.S. patent no. 4,792,452 to Howard et al., the entirety of the disclosure of which is hereby specifically incorporated by reference.

Specific examples of formulations of the invention which may be used with drugs other than verapamil are as follows:

<u>COMPONENT</u>		<u>AMOUNT OF COMPONENT IN EACH EMBODIMENT</u>	
		<u>A</u>	<u>B</u>
1. PENTOXYFILLINE		400 MG	600 MG
2. SODIUM ALGINATE		60 MG	80 MG
3. HYDROXYPROPYLETHYL CELLULOSE		50 MG	120 MG
4. EUDRAGIT®		20 MG	20 MG
5. POVIDONE		25 MG	40 MG
6. MICROCRYSTALLINE CELLULOSE		42 MG	55 MG
7. MAGNESIUM STEARATE		3 MG	5 MG

- 6 -

<u>COMPONENT</u>		<u>AMOUNT OF COMPONENT IN EACH EMBODIMENT</u>	
		<u>A</u>	<u>B</u>
	1. NIFEDIPINE	90 MG	60 MG
5	2. SODIUM CARBOXY METHYL CELLULOSE	30 MG	12 MG
	3. HYDROXY PROPYL METHYL CELLULOSE	30 MG	36 MG
	4. CELLULOSE ACETATE PHTHALATE	10 MG	12 MG
10	5. POVIDONE	16 MG	14 MG
	6. LACTOSE	112 MG	74 MG
	7. MICROCRYSTALLINE CELLULOSE	30 MG	30 MG
	8. MAGNESIUM STEARATE	2 MG	2 MG

15 Tablets based on the formulations described above incorporating pentoxifylline and nifedipine may be prepared using procedures which are essentially the same as the procedure described previously for preparing tablets based on formulations incorporating verapamil.

- 7 -

WE CLAIM:

1. A tablet for sustained release of a drug comprising an effective amount of a drug to be released at a controlled rate and a sustained release formulation, said sustained release formulation comprising at least three different types polymers including a pH dependent gelling polymer, a pH independent gelling polymer and an enteric polymer.
2. A tablet as set forth in claim 1, wherein said pH dependent gelling polymer comprises one or more of an alginate, a carboxyvinyl polymer and a salt of a carboxymethyl cellulose.
3. A tablet as set forth in claim 1, wherein said pH independent gelling polymer comprises one or more of a hydroxy propyl methyl cellulose, a hydroxy propyl ethyl cellulose, a hydroxy propyl cellulose, a hydroxy ethyl cellulose, a methyl cellulose, a xantham gum or a polyethylene oxide.
4. A tablet as set forth in claim 1, wherein said enteric polymer comprises one or more of a polyacrylate material, a cellulose acetate phthalate, a cellulose phthalate hydroxy propyl methyl ether, a polyvinyl acetate phthalate, a hydroxy propyl methyl cellulose acetate succinate, a cellulose acetate trimellitate, or a shellac.
5. A tablet as set forth in claim 4, wherein said polyacrylate material comprises a methacrylic acid copolymer.
6. A tablet as set forth in claim 5, wherein said methacrylic acid copolymer is Eudragit® L.
7. A tablet as set forth in claim 5, wherein said methacrylic acid copolymer is Eudragit® S.
8. A tablet as set forth in claim 1, wherein said drug comprises one or more of a water soluble, water sparingly soluble or water insoluble active material.

- 8 -

9. A tablet as set forth in claim 1, wherein the content of said drug in said formulation ranges from about 0.5% to about 70% by weight thereof.

10. A tablet as set forth in claim 1, wherein the total content of said gelling and enteric polymers in said formulation ranges from about 8% to about 65% by weight thereof.

11. A tablet as set forth in claim 1, wherein the content of said pH dependent gelling polymer in said formulation ranges from about 2% to about 60% by weight thereof.

12. A tablet as set forth in claim 1, wherein the content of said pH independent gelling polymer in said formulation ranges from about 2% to about 55% by weight thereof.

13. A tablet as set forth in claim 1, wherein the content of said enteric polymer in said formulation ranges from about 1% to about 55% by weight thereof.

14. A tablet for sustained release of an active material comprising a sustained release formulation, said sustained release formulation comprising at least three different types polymers including a pH dependent gelling polymer, a pH independent gelling polymer and an enteric polymer.

15. A formulation for sustained release of an active material, said sustained release formulation comprising at least three different types polymers including a pH dependent gelling polymer, a pH independent gelling polymer and an enteric polymer.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/25630

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/22

US CL :424/468

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/468

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,708,874 A (DE HAAN et al.) 24 November 1987, see claims 1, 8, 13, 16 and 25-28.	1-15

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

22 FEBRUARY 1999

Date of mailing of the international search report

02 MAR 1999

 Name and mailing address of the ISA/US
 Commissioner of Patents and Trademarks
 Box PCT
 Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

JAMES M. SPEAR

Telephone No. (703) 308-1235